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<p>(21) International Application Number: PCT/SE90/00886 (22) International Filing Date: 28 December 1990 (28.12.90) (30) Priority data: 8904407-7 29 December 1989 (29.12.89) SE (71)(72) Applicants and Inventors: HEDNER, Thomas [SE/SE]; Trumpetargränd 4, S-412 67 Göteborg (SE). FENG, Qingping [CN/SE]; Dr Lindhs gata 1, S-413 25 Göte- borg (SE). (74) Agents: STRÖM, Tore et al.; Ström & Gulliksson AB, Box 4188, S-203 13 Malmö (SE).</p>		<p>(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report.</i></p>
<p>(54) Title: MEDICAMENT FOR TREATMENT OF HEART FAILURE (57) Abstract The present invention relates to a combination of substances, firstly from the group of α-2-adrenergic agonists or other inhibitors of the sympathetic nervous system, and secondly from the group of natriuretic peptides (ANP, BNP, their pharmacologically active analogues, ANP C-receptor ligands, or inhibitors of degradation), this combination exhibiting a therapeutic diuretic and natriuretic effect in heart failure, not achievable with any substance from only one of the groups of substances.</p>		

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MEDICAMENT FOR TREATMENT OF HEART FAILURE

The present invention relates to previously not reported properties of the combination of a natural hormone, Atrial Natriuretic Peptide (ANP), also named
5 Atrial Natriuretic Factor (ANF), and known antihypertensive medicaments, known as α -2-adrenergic agonists, resulting in a therapeutic effect in heart failure, not attainable with only one of the components.

Through a combination of these substances, as
10 defined in this invention, a medicament is created which counteracts the symptoms in heart failure and increases the pumping capacity of the heart with a synergistic effect that cannot be obtained using the two substances separately.

15 General background of the inventionThe Pathophysiology of Heart Failure

Heart failure as a disorder, or rather as a syndrome, can be defined in many ways. The following definition (1) focuses on the impaired pumping capacity
20 of the heart: "Heart failure is the pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues".

25 Another definition (2) emphasizes the effects on the circulation for maintaining the required supply of oxygen and nutrients to the various organs, as well as the results of a disturbed hormonal balance: "Congestive heart failure is the failure of the heart to maintain
30 cardiac output at a level which is adequate to meet the metabolic demands of the tissues with preserved normal filling pressures, and with undisturbed neurohormonal and endocrine equilibrium".

Heart failure, therefore, is a condition not only
35 characterized by the impaired pumping capacity of the

heart, but also presenting a series of hemodynamic, neurohumoral and endocrine changes with negative consequences for the organism. In short, the organism with heart failure strives to adjust the blood circulation in order to sustain the supply of oxygen and nutrients to vital organs as adequate as possible. However, this adjustment of the blood circulation results in an increased work load on the heart, experienced by the patient as an aggravated breathlessness, when any strain is exerted.

In severe heart failure, particularly in the late stages of the disease, the patient suffers from great difficulties in performing even minor physical activities, as walking or even lying down in supine position, without experiencing suffocating breathlessness. Prognostically heart failure is a very serious condition, especially the stages graded New York Heart Association (NYHA) class 3-4. Patients in these categories, even under treatment presently available, have a 5-year survival rate comparable with rates recorded for many forms of advanced cancer.

One important factor contributing to the poor prognosis in heart failure is the mechanism of neurohumoral compensation affecting central nervous, cardiac, peripheral and endocrine systems. The neurohumoral compensation is characterized by an increased activity in the renin-angiotensin-aldosterone system and an increased secretion of vasopressin. In conditions with mild heart failure, this response will assist to sustain a normal perfusion of vital organs. However, in severe heart failure the response will tend to overcompensate and will seriously impair the peripheral circulation and tissue supply of essential nutrients and oxygen.

In cases of severe congestive heart failure an

exaggerated compensation of the renin-angiotensin-aldosterone system can be suppressed by administration of blocking drugs, e.g. inhibitors of renin, aldosterone or angiotensin converting enzyme (ACE). These drugs can
5 abate the symptoms of congestive heart failure and in some cases expand the time of survival. Many of these drugs can, however, cause adverse effects and the ACE-inhibitors, as they are called, occasionally induce a serious fall of the systemic blood pressure, at times
10 even leading to a circulatory collapse.

Other schemes for pharmacological treatment encompass drugs increasing the contractility of the heart, e.g. digitalis preparations and diuretics, remedies augmenting the excretion of water.

15 Vasodilatory drugs with peripheral action, e.g. calcium blockers and organic nitro preparations, have also been used in the treatment of heart failure.

Several natural humoral mechanisms for compensation tend to counteract the enhanced activity in the sympathetic nervous systems and the activation of the renin-angiotensin-aldosterone system. Such a mechanism which
20 was recently discovered, relates to the effect of a group of hormones produced by and excreted from the heart muscle cells. The most well-known of these hormones is
25 ANP (Atrial Natriuretic Peptide) also called ANF (Atrial Natriuretic Factor). This hormone induces a diuresis, inhibits the renin-angiotensin-aldosterone system and causes a mild vasodilatation.

In heart failure these effects are beneficial as
30 they strive to counteract mechanisms of overcompensation, resulting in an impaired peripheral circulation, often experienced in severe congestive heart failure. In cases of severe congestive heart failure, a continuously rising level of ANP in blood can be observed, most probably

reflecting an attempt by the heart muscle to adjust the abnormal neurohumoral balance. However, in spite of the rising levels of ANP in the blood no expected increase in diuresis or natriuresis will result.

5 Even exogenous ANP is virtually without effect and it is evident that patients with congestive heart failure cannot respond to ANP with the increase in diuresis and natriuresis, as seen in normal individuals (3,4). Obviously, patients with congestive heart failure somehow
10 develop a pharmacological tolerance against the positive effects normally exerted by the effects of circulating ANP.

The present invention describes our approach to resolve this problem and a method is outlined for
15 restoring the positive effects on circulation by ANP, also in patients with congestive heart failure.

Specific background to the invention

Previous experiments have shown that α -2-adrenergic agonists, in addition to hypotensive effects, also induce
20 diuresis and natriuresis in normal animals (5). Similar properties have also been ascribed to ANP and its analogues (6). In heart failure, however, a pharmacological tolerance develops against the diuretic and natriuretic effects of α -2-adrenergic agonists as well as
25 of ANP and its analogues. Any of these substances are thus ineffective when treating heart failure and used singly.

In the event of other oedematous disorders due to other diseases than heart failure, e.g. liver cirrhoses
30 and renal disease, these prove to be treatable with a combination of synthetic α -2-agonists (or other blockers of the sympathetic nervous system) in combination with ANP, BNP (Brain Natriuretic Peptide) or their analogues (alternatively ANP C-receptor ligands or inhibitors of

the degradation of ANP or BNP) as described in detail below. These disorders should be considered comparable to heart failure regarding the mechanisms and properties encompassed by the invention.

5 α -2-adrenergic agonists belong to a group of medicaments encompassing several chemical structures (7,8). The dominating pharmacological effect of an α -2-adrenergic agonist is a reversible stimulation of α -2-adrenergic receptors on the neural structures in the
10 peripheral and central nervous systems, thereby inhibiting the release of the transmitter-substance noradrenaline (NA). The most recognized substance with α -2-adrenergic agonist effects is clonidine. Its general chemical structure has been identified (8). Other
15 structures with similar principal effects as the clonidine-molecule have also been synthesized.

 The α -2-receptoragonists primarily included in this invention are the following preparations: methylopa, α -methyl-noradrenaline, clonidine, guanabenz and
20 guanfacine. The invention likewise includes newer substances with a similar mode of action as tramazoline, tolazoline, oximetazoline, nafazoline, oxaminozoline, rilmelidine, medetmoldine and detmoldine (MPV-253).

 To the extent that substances, chemically related
25 to the preparations described above, act in a similar way in combination with ANP, BNP, their active analogues, ANP C-receptor ligands and inhibitors of their degradation according to the description below, these substances should be considered as identical with the specified α -2-receptoragonists as far as the properties included in
30 this invention are concerned.

 Clonidine, or any other of the α -2-receptor agonists described, is administered in a pharmaceutically acceptable form of an atoxic salt, e.g. as chloride,

sulphate, nitrate, phosphate, acetate, tartrate, citrate, fumarate, maleate, toluensulfonate, methansulfonate or as halide.

Even if it should be possible to administer the described α -2-receptoragonists or their pharmaceutically acceptable salts as a substance, they are in principal always given as a pharmaceutical preparation. This pharmaceutical preparation is composed of the active substance in combination with an acceptable carrier. This carrier has to be "acceptable" in the sense that it should be compatible with the other ingredients included and it must not cause harm or induce other negative effects when administered. The preparations referred to in this invention should be possible to produce with utilization of known pharmaceutical techniques.

The pharmaceutical preparations include preparations for oral administration such as e.g. tablets, capsules, mixtures, slow release or extended release preparations. Furthermore, intravenous, intramuscular or subcutaneous preparations as well as pharmaceutical preparations for regional administration such as e.g. rectal, vaginal, ocular, nasal, inhalational, epidural and spinal administration is included in the invention.

In case of the pharmaceutical preparation being administered topically as for example as a spray, ointment, cream, gel or depot preparation, the carrier can contain one or more of the following substances: vaseline, lanoline, polyethylene glycols, glycols, beewax, mineral oil or other suitable vehicles. The preparation can also include solvents as water and alcohol, emulsifiers, stabilizers or other suitable substances.

A selective inhibition of the sympathetic nervous system can also be achieved using other means than

through activation of the α -2-adrenergic receptors. Through a specific inhibition of the release of noradrenaline from the nerve terminals using e.g. bretylium, betanidine or debrisoquine, an effective
5 blockage of the sympathetic nervous system can be attained. A similar repression of the sympathetic activity can also be reached through a specific inhibition of the synthesis of noradrenaline using - methyltyrosine or FLA-63, or by activating 5 HT receptors
10 of the 1A subtype by e.g. 8 OH-DPAT or flesinoxane.

Natriuretic peptides released from the heart muscle cells include ANP (Atrial Natriuretic Peptide), consisting of 28 amino acids (NH₂-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-
15 Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-COOH), containing a connecting double bond between the two Cys and a BNP (Brain Natriuretic Peptide) with a somewhat longer sequence of amino acids (6,10).

The first to be identified and the most extensively
20 studied member of the group of peptides with diuretic and natriuretic effects is ANP. Its general structure has been known since 1984 (6). Since ANP has a very short half-life, only about 1-2 minutes, with very poor or non-existent peroral absorption, synthesized analogues of ANP
25 with longer duration and more favourable absorption characteristics were sought. By these efforts structures could be synthesized possessing the same principal pattern, as well as mode of action and effects, as the endogenous natriuretic peptides (10).

30 ANP and its bioactive analogues act through a biological receptor, which is bound to particulate guanylate cyclase (GC), termed the B-receptor (10). In addition to the B-receptor there is a clearance site (C-receptor) which is biologically inactive, i.e. not bound

to GC, and acts as a clearance receptor, which internalizes bound ANP for lysosomal degradation (10). Synthetic compounds which occupy the C-receptor increase the concentrations of circulating ANP and may thus have a therapeutic potential. Such a substance is for example
5 [des Phe106-Gly107-Ala108-Asp116] -ANP(103-126) or SC-46542.

Some chemical substances blocking the enzyme (Neutral Endo Peptidase-NEP 24.11; EC 3.4.24.11) primarily responsible for the degradation of ANP and BNP, can
10 also increase the concentrations of circulating endogenous ANP and BNP, respectively (10). Examples of such substances are for example SHC 32615, SCH 34826, SCH 39370, SQ 29072, tiorfan and UK 69578.

To the extent that synthetic analogues of ANP, BNP, ANP C-receptor ligands or inhibitors of ANP degradation in combination with α -2-adrenergic agonists or other blockers of sympathetic nervous activity act in a similar way as in combination with natural ANP, as described in
15 20 detail below, those substances should be considered as identical with ANP concerning the properties and effects encompassed by this invention.

Detailed description of the invention

The aim of the present invention is to master the pharmaceutical tolerance (decreased responsiveness) for
25 ANP or related natriuretic peptides developing in congestive heart failure and other oedematous disorders. Due to this pharmaceutical tolerance, the organism cannot adequately regulate the balance of the circulating volume
30 in these pathophysiological conditions, resulting in a retention of water and salts, known as oedema, and progressive heart failure.

The present invention implies the administration of a combination of chemical substances, firstly from the

group of α -2-adrenergic agonists or other inhibitors of sympathetic nerve activity and, secondly, from the group of natriuretic peptides (C-receptor ligands or the degradation blockers) which singly do not possess any adequate diuretic or natriuretic effect in congestive heart failure.

We have found that clonidine and its pharmaceutical active salts exhibit favourable qualities for augmenting or normalizing the diuretic and natriuretic effects of ANP. These results of the combination treatment have been documented in experimental models of heart failure in animals. It has been demonstrated by us that the properties of clonidine, as referred to in this invention, become active in the lower range of doses normally used for inducing pharmacological effects.

Recommended standard doses of clonidine in cardiovascular disorders, particularly hypertensive conditions, are related to the stage of the disease and to the mode of administration of the drug. Clonidine given perorally is well absorbed and the dose can thus principally be the same in peroral and systemic administration, i.e. 75 to 900 microgram per 24 hours or 1 to 100 microgram/kg/24 hours for a man weighing 70 kg. By local application (preferentially from a depot in a transdermal therapeutic system as described below) doses of 100-300 microgram per 24 hours can be administered to a patient (8, 9).

The diuretic and natriuretic effect of ANP has been investigated in control groups of normal, healthy subjects using various doses (from injection in high doses of 100 microgram to infusion in low doses of 0.05 microgram/kg/hour) (11). High single doses, as well as low continuous infusions, induce an increase in volume of urine passed and enhance the excretion of sodium in subjects without any heart disease.

However, in patients suffering from congestive heart failure, a drastically reduced or completely blunted effect of exogenous ANP has been observed and a researcher within the field (11) concludes: "The lack of natriuretic effect of ANP in heart failure is not well understood".

The present invention allows us to offer a previously not known explanation of this phenomenon, showing that a combination of a low dose of for example an α -2-adrenergic agonist and for example ANP will restore the normal diuretic and natriuretic response of for example ANP, otherwise lost in congestive heart failure.

These effects have been documented by us in the investigations described below, using animals in an experimental model simulating heart failure in man.

Clonidine restores diuresis and natriuresis induced by ANP in rats with ischemic heart failure

The experiments were conducted on 30 male Sprague-Dawley rats weighing 250-350 g. During Mebumal anesthesia the rats were intubated and artificially ventilated with a respirator. A left thoracotomy was performed, exposing the heart. We ligated the left coronary artery by positioning a suture between the pulmonary artery outflow tract and the left atrium. The lungs were then hyperinflated using positive end-expiratory pressure and the thoracic wall was sutured. The rats were allowed to recover for four weeks while a chronic heart failure condition developed.

During this period approximately half the numbers of rats died early from ventricular arrhythmia or severe heart failure. At the end of the experiment a postmortem examination was conducted on the remaining experimental animals (16 in all). The autopsy revealed a tissue destruction affecting approximately 35% of the total

circumference of the ventricle, leading to the severe heart failure observed.

Experiments were then performed in conscious animals, four weeks after the operation described above. During short-lasting anesthesia, each animal was furnished with an arterial catheter and with a catheter in the urinary bladder. The animals were placed in separate cages and after a short period for stabilization an infusion of saline was started in all animals. After one hour, half the numbers of rats received an infusion of clonidine (5 microgram/hour) and the other half received saline only (1.2 ml/hour for four hours).

During the infusion of clonidine, a minimal transient increase in urinary volume was recorded. The excretion of sodium and potassium was, however, not affected. The arterial blood pressure and the heart rate was depressed by approximately 10% at the end of the four-hour clonidine infusion, compared with the control group receiving saline.

After this four-hour infusion of either saline or clonidine both groups of animals with heart failure were given increasing doses of ANP: 0.25, 0.5 and 1.0 microgram/kg/hour during 15 minutes for each dose interval.

In the control group, previously treated only with saline, no significant increase in urinary volume or in the excretion of potassium was observed, while the excretion of sodium was doubled.

The group of rats treated with clonidine, on the other hand, showed a 4-5 time increase of the urine volume already at the lowest dose administered. The excretion of sodium was augmented in the same order of magnitude, while the outflow of potassium increased only 0.5 times. The relative changes in arterial blood pressure and heart rate were similar in both groups.

This experiment on rats with severe heart failure clearly demonstrates that the pharmaceutical tolerance developing for ANP in connection with congestive heart failure can be reversed by an inhibition of the sympathetic nervous system. The effects recorded after treatment with clonidine are in general identical with the effects observed in normal rats without heart failure.

This effect of a combined treatment, previously not described, should be of great medical interest in the treatment of patients with severe congestive heart failure.

Combinations of pharmaceutical preparations from the groups of substances, which therapeutic effects have been described in detail above, can be administered to patients via systemic, oral, sublingual, buccal, nasal, rectal, or topical (transdermal) routes. The following types of pharmaceutical preparations can be mentioned as examples according to the invention: solution, suspension, emulsion, ointment, cream, powder, spray, clyisma or suppository. Pharmaceutical preparations for parenteral use can encompass sterile solutions or suspensions of the active substance(s) in water or other suitable vehicles.

Peroral preparations can include a solution, capsule, tablet or similar, together with a pharmaceutically applicable vehicle. Preparations in the form of suppositories can also be appropriate.

Among proper depot preparations mention can be made especially of the transdermal therapeutic system (TTS), as it is called, based on multilaminar plaster preparations. This system consists of a rear impermeable part, one polymer based reservoir of the active drug, a microporous membrane and finally an adhesive layer

closest to the skin, containing the "priming dose" of the active substance or combination of substances in question (9).

CLAIMS

1. A medicament with a therapeutic combination effect in heart failure or comparable oedematous disorders, characterised by its combination of pharmacologically active substances, firstly from the group of α -2-adrenergic agonists or other inhibitors of the sympathetic nervous system and, secondly, from the group of natriuretic peptides (ANP, BNP or their active analogues), alternatively ANP C-receptor ligands or inhibitors of the enzyme neutral endopeptidase (NEP 24.11; EC 3.4.24.11).

2. A medicament according to claim 1, characterised by its content, as the first component (inhibiting the sympathetic nervous system), of methyldopa, clonidine, guanabenz, guanfacine, idazoxan, tolazoline, oxaminoxoline, medetomidine, detomidine (MPV-253, bretylium, betanidine, debrisoquine, α -methyl-tyrosine or FLA-63.

3. A medicament according to claim 1, characterised by its content, as the second component, of the endogenous peptide ANP (Atrial Natriuretic Peptide), amino acid sequence NH_2 -Ser-Leu-Arg-Arg-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-COOH, with a connecting double bond between the two Cys, or BNP (Brain Natriuretic peptide), alternatively their pharmacologically active analogues, an ANP C-receptor ligand such as e.g. SC-46542, or inhibitors of the enzyme (Neutral Endo Peptidase- NEP 24.11; EC 3.4.24.11), primarily responsible for the degradation of ANP and BNP, the inhibitors in question being e.g. SCH 32615, SCH 344826, SHC 39370, SQ 290072, tiorfan and UK 69578.

4. A medicament according to any of claims 1-3, characterised by its presence in the form of

a pharmaceutically suitable preparation.

5 5. A medicament according to any of claims 1-4,
c h a r a c t e r i s e d by its content of pharmaceut-
ically active amounts of one or several of the substances
according to claims 2-3.

10 6. A medicament according to any of claims 1-5,
c h a r a c t e r i s e d by its content of one or
several inert carriers, suitable for systemic, that is
intravascular (intravenous or intraarterial), or extra-
vasacular (e.g. intramuscular or subcutaneous)
administration to a patient.

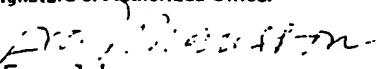
15 7. A medicament according to any of claims 1-5,
c h a r a c t e r i s e d by its content of one or
several inert carriers, suitable for topical or trans-
cutaneous administration to a patient.

20 8. A medicament according to any of claims 1-5,
c h a r a c t e r i s e d by its content of one or
several inert carriers, suitable for peroral administra-
tion to a patient.

20 9. A medicament according to any of claims 1-8,
c h a r a c t e r i s e d by its form, regarding shape
or enclosure in any medium, aiming at a sustained
release, whereby the medicament after administration will
exert its effect during a prolonged period of time.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00886

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 45/06		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	Acta Physiol Scand, Vol. 135, 1989 A. Pettersson et al.: "Relationship between renal sympathetic activity and diuretic effects of atrial natriuretic peptide (ANP) in the rat", see page 323 - page 333 --	1-9
A	ActaPhysiol Scand, Vol. 126, 1986 A. Pettersson et al.: "The diuretic effect of atrial natriuretic peptide (ANP) is dependent on dopaminergic activation", see page 619 - page 621 --	1-9
A	The American Journal of Cardiology, Vol. 62, July 1988 Gary S. Francis: "Neuroendocrine Manifestations of Congestive Heart Failure", see page 9A - page 13A --	1-9
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
2nd April 1991	1991 -04- 15	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	 E. Johansson	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	<p>Journal of Cardiovascular Pharmacology, Vol. 14, No. 8, 1989 Gabriella Cargnelli et al.: "Present and Future Trends in Research and Clinical Applications of Inodilators", see page 124 - page 132 see particularly page 128</p> <p>--</p> <p>-----</p>	1-9